Ibogaine in the Treatment of Alcoholism:

A Randomized, Double-blind, Placebo-controlled, Escalating-dose, Phase 2 Trial

Prof. Dr. Rafael Guimarães dos Santos

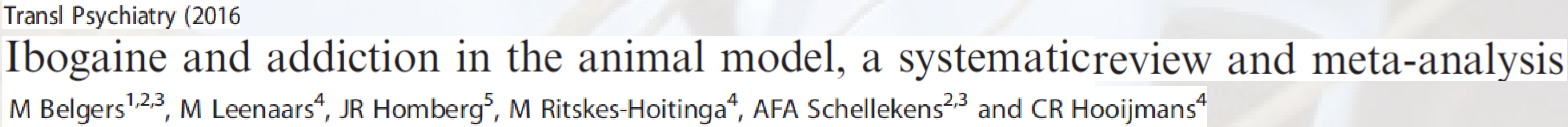
Dep. Neurosciences and Behaviour
Ribeirão Preto Medical School
University of São Paulo (Brazil)

ICEERS Foundation (Spain)

The European Ibogaine Forum 2018

by Cures Not Wars

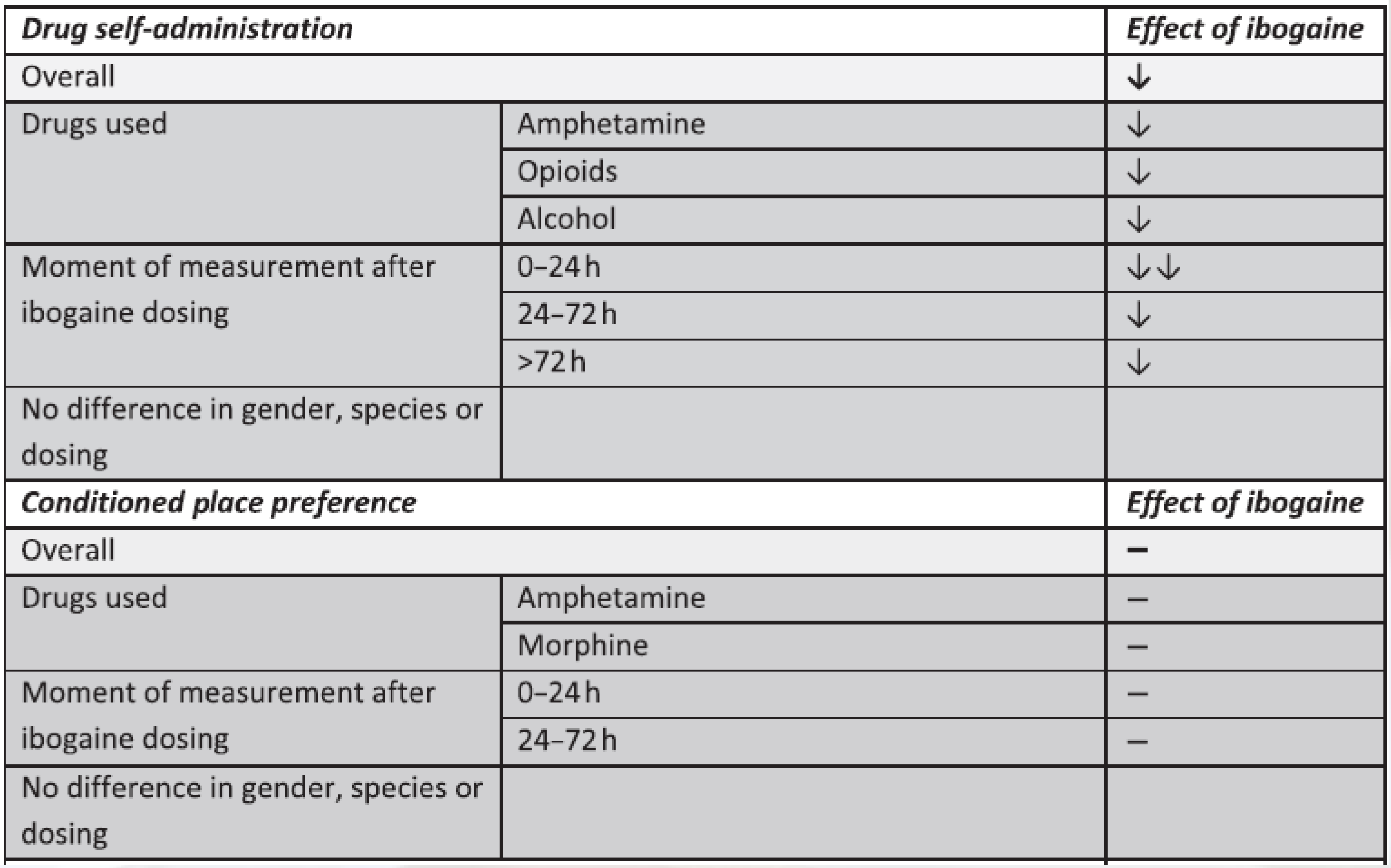
Preclinical Studies



Transl Psychiatry (2016

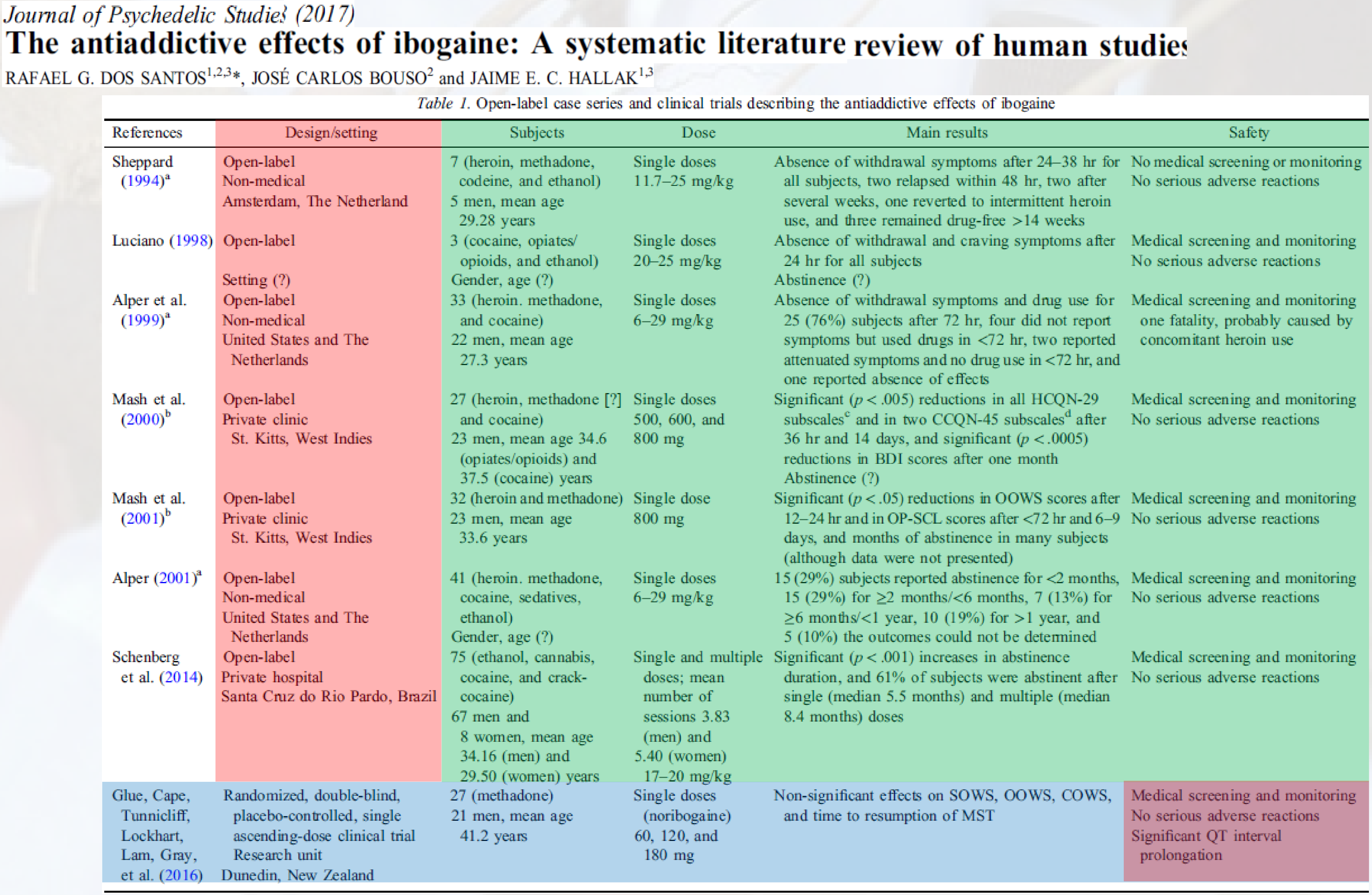
Ibogaine and addiction in the animal model, a systematicreview and meta-analysis

M Belgers[1,2,3], M Leenaars[4], JR Homberg[5], M Ritskes-Hoitinga[4], AFA Schellekens[2,3] and CR Hooijmans[4]



Drug self-administration		***Effect of ibogaine***
Overall		↓
Drugs used	Amphetamine	↓
	Opioids	↓
	Alcohol	↓
Moment of measurement after ibogaine dosing	0–24 h	↓↓
	24–72 h	↓
	>72 h	↓
No difference in gender, species or dosing		
Conditioned place preference		***Effect of ibogaine***
Overall		–
Drugs used	Amphetamine	–
	Morphine	–
Moment of measurement after ibogaine dosing	0–24 h	–
	24–72 h	–
No difference in gender, species or dosing		

Human Studies



Journal of Psychedelic Studies (2017)

The antiaddictive effects of ibogaine: A systematic literature review of human studies

RAFAEL G. DOS SANTOS[1,2,3]*, JOSÉ CARLOS BOUSO[2] and JAIME E. C. HALLAK[1,3]

Table 1. Open-label case series and clinical trials describing the antiaddictive effects of ibogaine

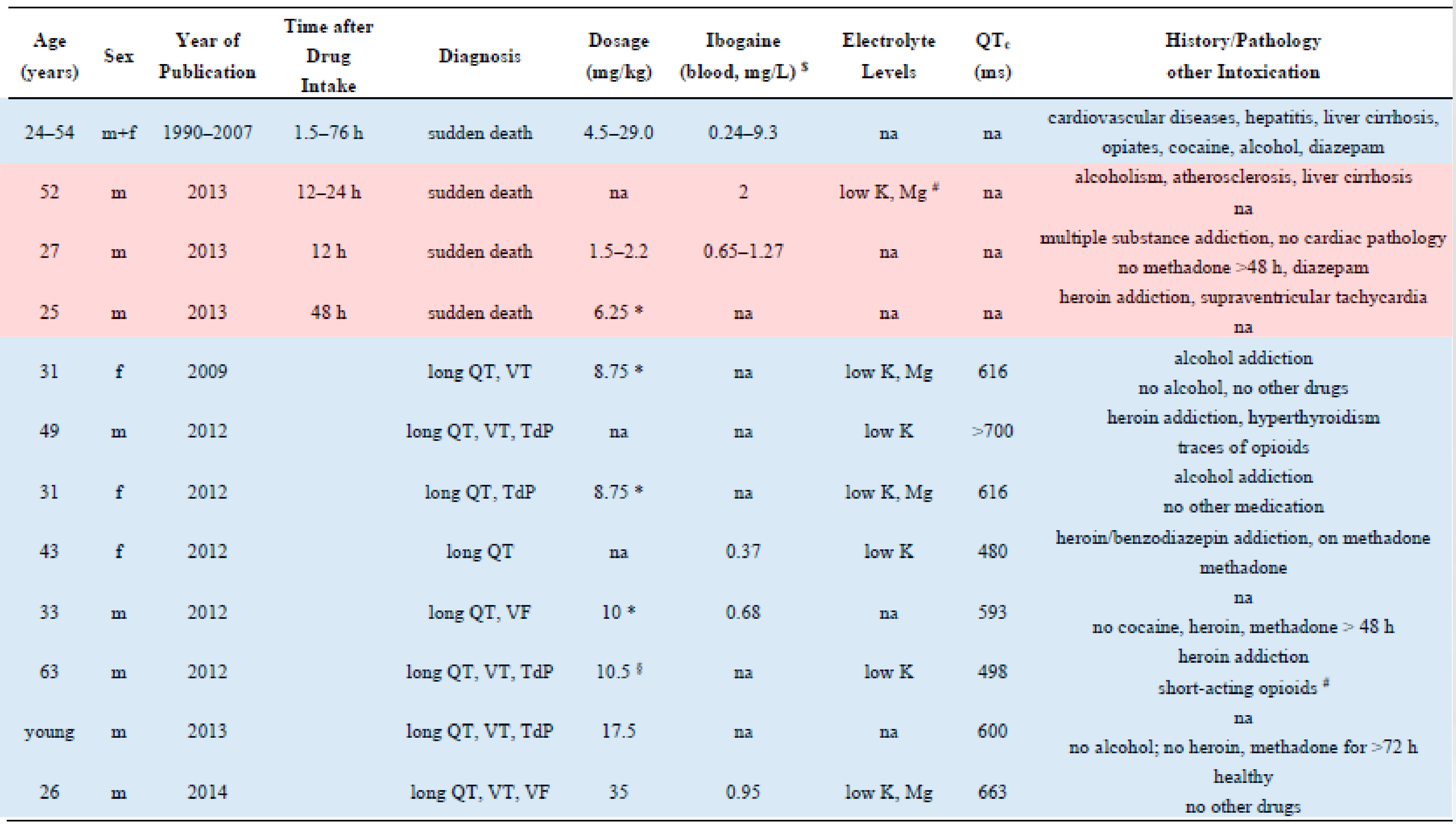
References	Design/setting	Subjects	Dose	Main results	Safety
Sheppard (1994)[a]	Open-label Non-medical Amsterdam, The Netherland	7 (heroin, methadone, codeine, and ethanol) 5 men, mean age 29.28 years	Single doses 11.7–25 mg/kg	Absence of withdrawal symptoms after 24–38 hr for all subjects, two relapsed within 48 hr, two after several weeks, one reverted to intermittent heroin use, and three remained drug-free >14 weeks	No medical screening or monitoring No serious adverse reactions
Luciano (1998)	Open-label Setting (?)	3 (cocaine, opiates/opioids, and ethanol) Gender, age (?)	Single doses 20–25 mg/kg	Absence of withdrawal and craving symptoms after 24 hr for all subjects Abstinence (?)	Medical screening and monitoring No serious adverse reactions
Alper et al. (1999)[a]	Open-label Non-medical United States and The Netherlands	33 (heroin. methadone, and cocaine) 22 men, mean age 27.3 years	Single doses 6–29 mg/kg	Absence of withdrawal symptoms and drug use for 25 (76%) subjects after 72 hr, four did not report symptoms but used drugs in <72 hr, two reported attenuated symptoms and no drug use in <72 hr, and one reported absence of effects	Medical screening and monitoring one fatality, probably caused by concomitant heroin use
Mash et al. (2000)[b]	Open-label Private clinic St. Kitts, West Indies	27 (heroin, methadone [?] and cocaine) 23 men, mean age 34.6 (opiates/opioids) and 37.5 (cocaine) years	Single doses 500, 600, and 800 mg	Significant ($p < .005$) reductions in all HCQN-29 subscales[c] and in two CCQN-45 subscales[d] after 36 hr and 14 days, and significant ($p < .0005$) reductions in BDI scores after one month Abstinence (?)	Medical screening and monitoring No serious adverse reactions
Mash et al. (2001)[b]	Open-label Private clinic St. Kitts, West Indies	32 (heroin and methadone) 23 men, mean age 33.6 years	Single dose 800 mg	Significant ($p < .05$) reductions in OOWS scores after 12–24 hr and in OP-SCL scores after <72 hr and 6–9 days, and months of abstinence in many subjects (although data were not presented)	Medical screening and monitoring No serious adverse reactions
Alper (2001)[a]	Open-label Non-medical United States and The Netherlands	41 (heroin. methadone, cocaine, sedatives, ethanol) Gender, age (?)	Single doses 6–29 mg/kg	15 (29%) subjects reported abstinence for <2 months, 15 (29%) for ≥2 months/<6 months, 7 (13%) for ≥6 months/<1 year, 10 (19%) for >1 year, and 5 (10%) the outcomes could not be determined	Medical screening and monitoring No serious adverse reactions
Schenberg et al. (2014)	Open-label Private hospital Santa Cruz do Rio Pardo, Brazil	75 (ethanol, cannabis, cocaine, and crack-cocaine) 67 men and 8 women, mean age 34.16 (men) and 29.50 (women) years	Single and multiple doses; mean number of sessions 3.83 (men) and 5.40 (women) 17–20 mg/kg	Significant ($p < .001$) increases in abstinence duration, and 61% of subjects were abstinent after single (median 5.5 months) and multiple (median 8.4 months) doses	Medical screening and monitoring No serious adverse reactions
Glue, Cape, Tunnicliff, Lockhart, Lam, Gray, et al. (2016)	Randomized, double-blind, placebo-controlled, single ascending-dose clinical trial Research unit Dunedin, New Zealand	27 (methadone) 21 men, mean age 41.2 years	Single doses (noribogaine) 60, 120, and 180 mg	Non-significant effects on SOWS, OOWS, COWS, and time to resumption of MST	Medical screening and monitoring No serious adverse reactions Significant QT interval prolongation

Adverse Reactions

Molecules **2015**

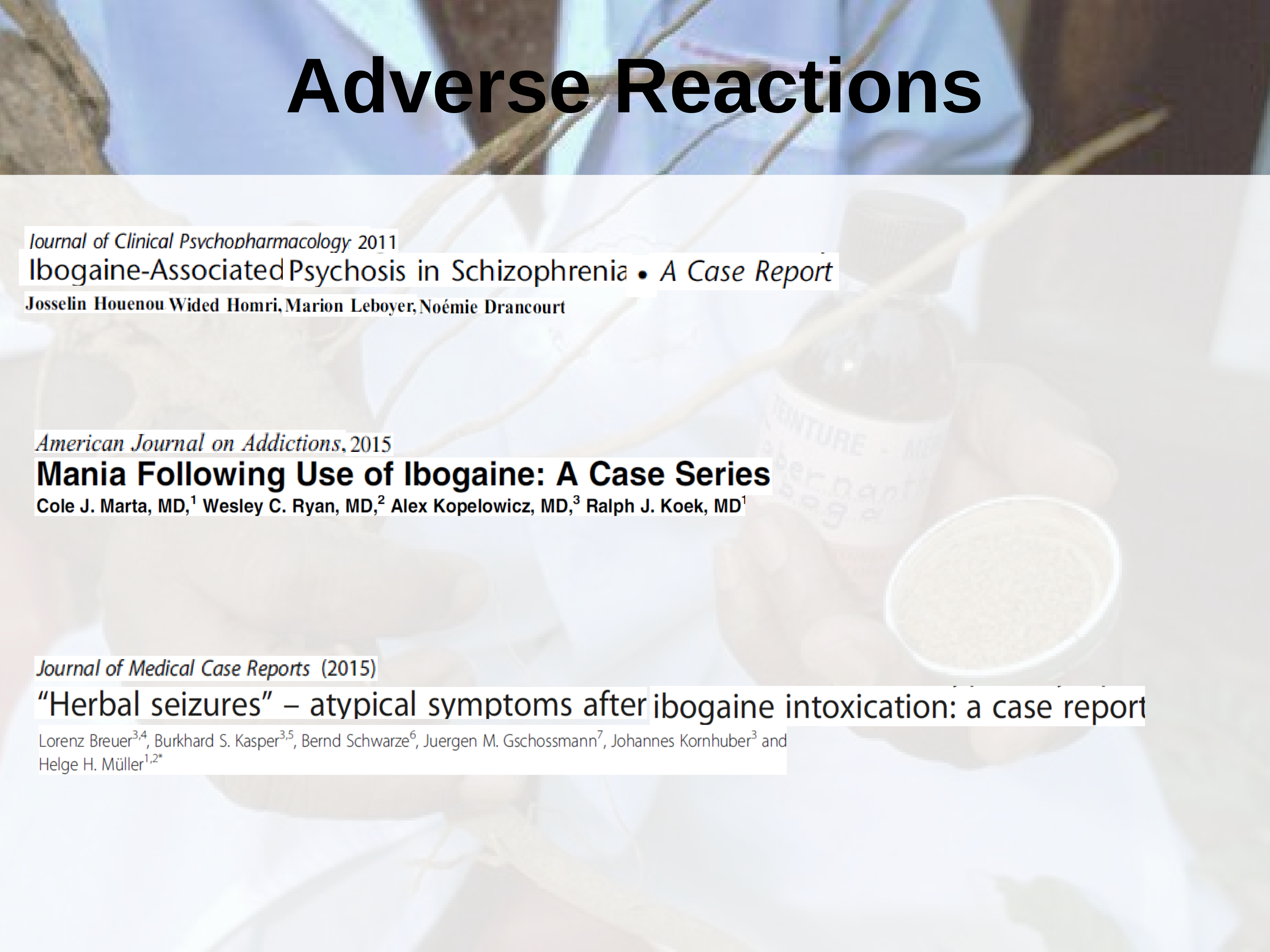
The Anti-Addiction Drug Ibogaine and the Heart: A Delicate Relation

Xaver Koenig * and Karlheinz Hilber *



Age (years)	Sex	Year of Publication	Time after Drug Intake	Diagnosis	Dosage (mg/kg)	Ibogaine (blood, mg/L) $	Electrolyte Levels	QT$_c$ (ms)	History/Pathology other Intoxication
24–54	m+f	1990–2007	1.5–76 h	sudden death	4.5–29.0	0.24–9.3	na	na	cardiovascular diseases, hepatitis, liver cirrhosis, opiates, cocaine, alcohol, diazepam
52	m	2013	12–24 h	sudden death	na	2	low K, Mg #	na	alcoholism, atherosclerosis, liver cirrhosis na
27	m	2013	12 h	sudden death	1.5–2.2	0.65–1.27	na	na	multiple substance addiction, no cardiac pathology no methadone >48 h, diazepam
25	m	2013	48 h	sudden death	6.25 *	na	na	na	heroin addiction, supraventricular tachycardia na
31	f	2009		long QT, VT	8.75 *	na	low K, Mg	616	alcohol addiction no alcohol, no other drugs
49	m	2012		long QT, VT, TdP	na	na	low K	>700	heroin addiction, hyperthyroidism traces of opioids
31	f	2012		long QT, TdP	8.75 *	na	low K, Mg	616	alcohol addiction no other medication
43	f	2012		long QT	na	0.37	low K	480	heroin/benzodiazepin addiction, on methadone methadone
33	m	2012		long QT, VF	10 *	0.68	na	593	na no cocaine, heroin, methadone > 48 h
63	m	2012		long QT, VT, TdP	10.5 §	na	low K	498	heroin addiction short-acting opioids #
young	m	2013		long QT, VT, TdP	17.5	na	na	600	na no alcohol; no heroin, methadone for >72 h
26	m	2014		long QT, VT, VF	35	0.95	low K, Mg	663	healthy no other drugs

Adverse Reactions



Journal of Clinical Psychopharmacology 2011

Ibogaine-Associated Psychosis in Schizophrenia • *A Case Report*

Josselin Houenou, Wided Homri, Marion Leboyer, Noémie Drancourt

American Journal on Addictions, 2015

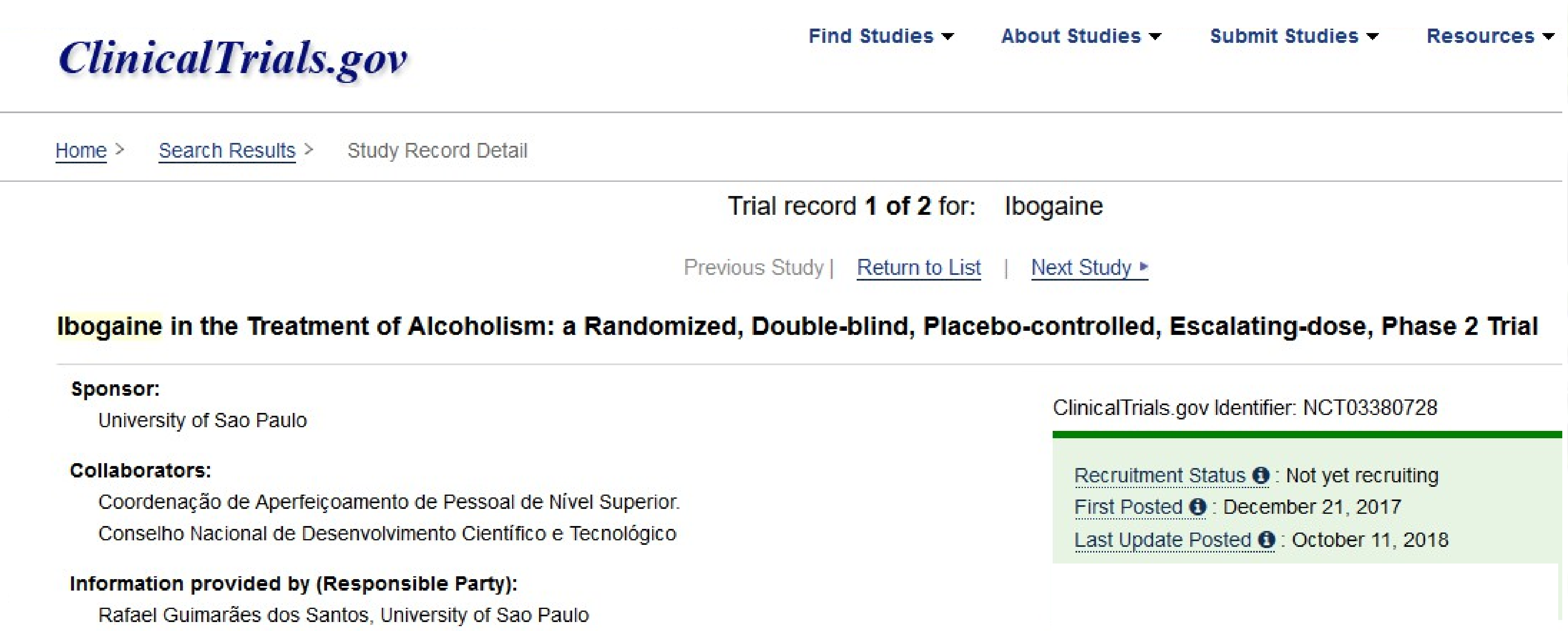
Mania Following Use of Ibogaine: A Case Series

Cole J. Marta, MD,[1] Wesley C. Ryan, MD,[2] Alex Kopelowicz, MD,[3] Ralph J. Koek, MD[1]

Journal of Medical Case Reports (2015)

"Herbal seizures" – atypical symptoms after ibogaine intoxication: a case report

Lorenz Breuer[3,4], Burkhard S. Kasper[3,5], Bernd Schwarze[6], Juergen M. Gschossmann[7], Johannes Kornhuber[3] and Helge H. Müller[1,2*]



Trial record **1 of 2** for: Ibogaine

Ibogaine in the Treatment of Alcoholism: a Randomized, Double-blind, Placebo-controlled, Escalating-dose, Phase 2 Trial

Sponsor:

University of Sao Paulo

Collaborators:

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.
Conselho Nacional de Desenvolvimento Científico e Tecnológico

Information provided by (Responsible Party):

Rafael Guimarães dos Santos, University of Sao Paulo

ClinicalTrials.gov Identifier: NCT03380728

Recruitment Status : Not yet recruiting
First Posted : December 21, 2017
Last Update Posted : October 11, 2018

Universidade de São Paulo

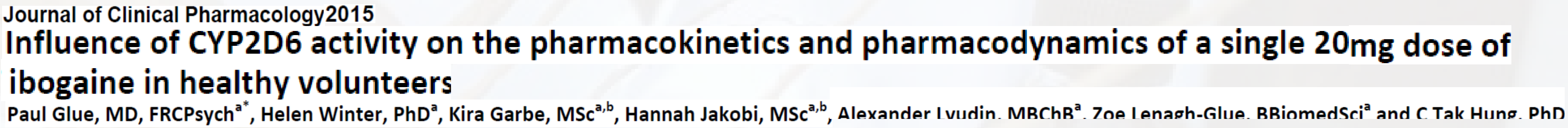
ICEERS

FAPESP

CAPES
Coordenação de Aprefeiçoamento de Pessoal de Nível Superior

CNPq

Rationale

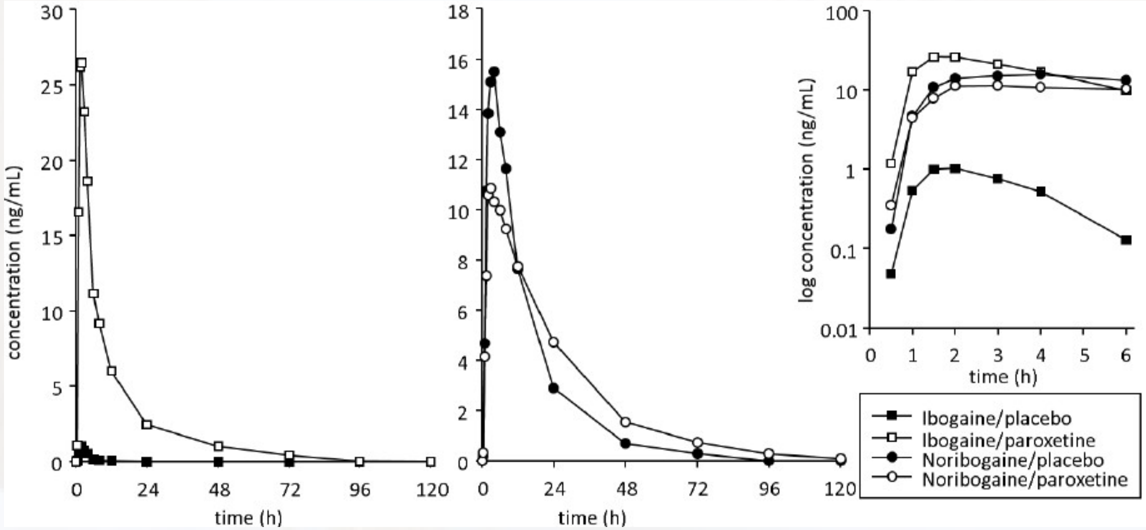


Journal of Clinical Pharmacology2015

Influence of CYP2D6 activity on the pharmacokinetics and pharmacodynamics of a single 20mg dose of ibogaine in healthy volunteers

Paul Glue, MD, FRCPsych[a*], Helen Winter, PhD[a], Kira Garbe, MSc[a,b], Hannah Jakobi, MSc[a,b], Alexander Lyudin, MBChB[a], Zoe Lenagh-Glue, BBiomedSci[a] and C Tak Hung, PhD

Single 20 mg ibogaine doses were safe and well tolerated in all subjects.



Rationale

Journal of Ethnopharmacology (2016)

Effects of low dose ibogaine on subjective mood state and psychological performance

Bridget Forsyth[a], Liana Machado[a], Tim Jowett[b], Hannah Jakobi[c,e], Kira Garbe[c,e], Helen Winter[d], Paul Glue[c,*]

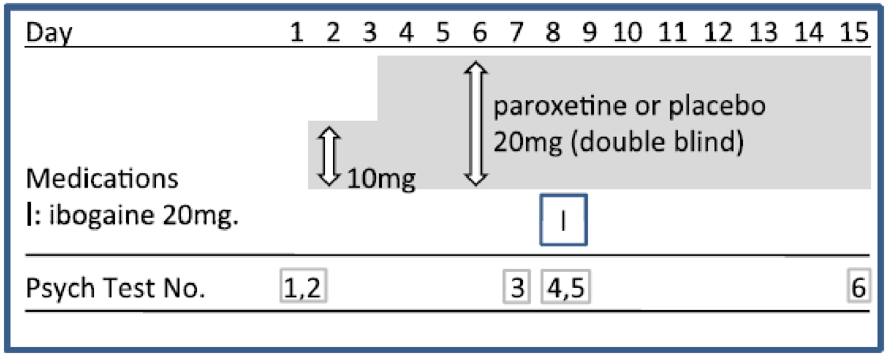
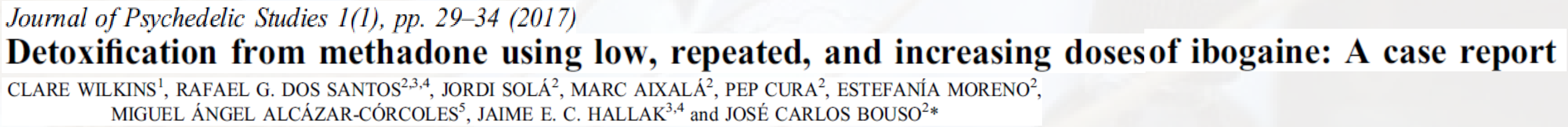


Fig. 1. Study design diagram. Subjects received double-blind capsules containing either paroxetine or placebo from Days 2–15. All subjects received open-label ibogaine on Day 8 at 8am. Psychological testing occurred twice on Day 1 at 10am and 12 noon; on Day 7 at 10am; on Day 8 at 10am and 12 noon; and on Day 15.

Results: Ibogaine had minimal influence on psychological tests and mood ratings. The ability to selectively ignore distracting spatial information showed some evidence of modulation; however because this effect was limited to the less challenging condition calls into question the reliability of this result. We were unable to identify stimulant effects after single 20 mg doses of ibogaine.

Rationale



Journal of Psychedelic Studies 1(1), pp. 29–34 (2017)

Detoxification from methadone using low, repeated, and increasing doses of ibogaine: A case report

CLARE WILKINS[1], RAFAEL G. DOS SANTOS[2,3,4], JORDI SOLÁ[2], MARC AIXALÁ[2], PEP CURA[2], ESTEFANÍA MORENO[2],
MIGUEL ÁNGEL ALCÁZAR-CÓRCOLES[5], JAIME E. C. HALLAK[3,4] and JOSÉ CARLOS BOUSO[2]*

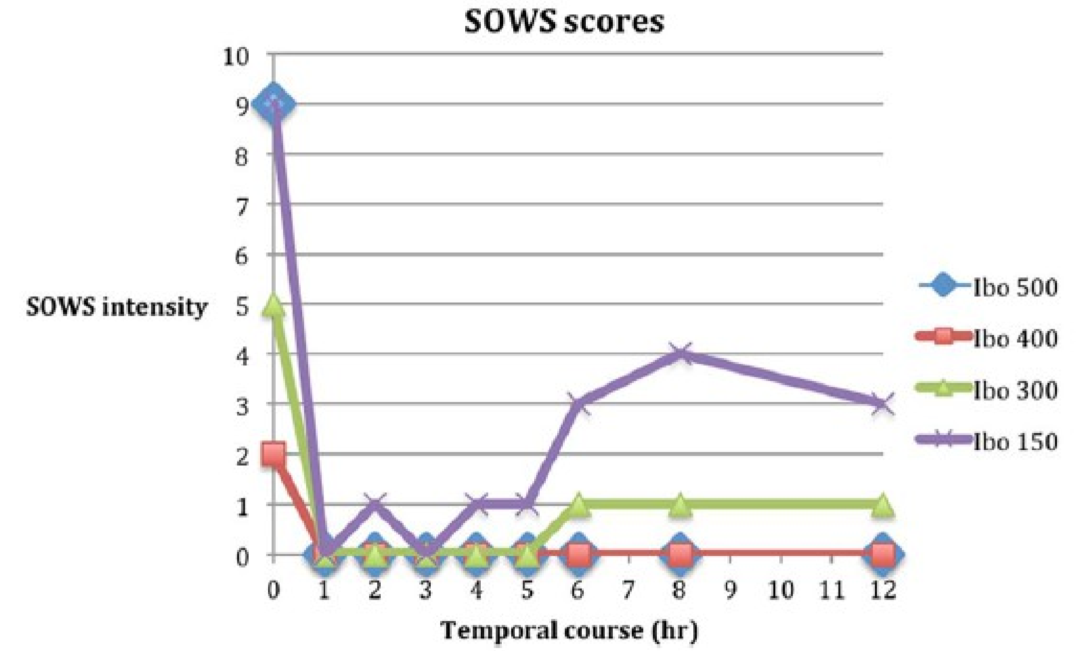
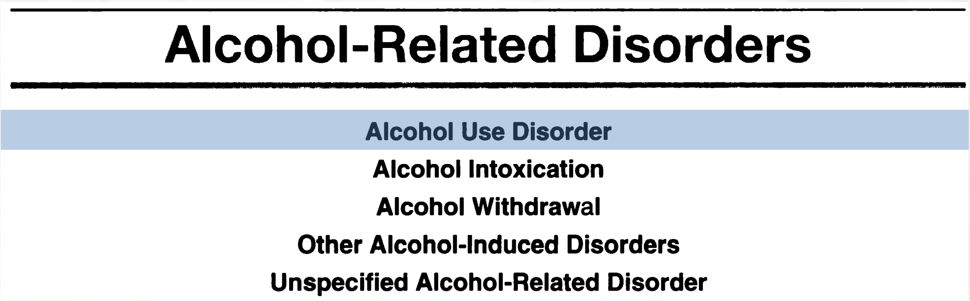


Figure 1. Short Opiate Withdrawal Scale (SOWS) scores for every ibogaine dose after its administration

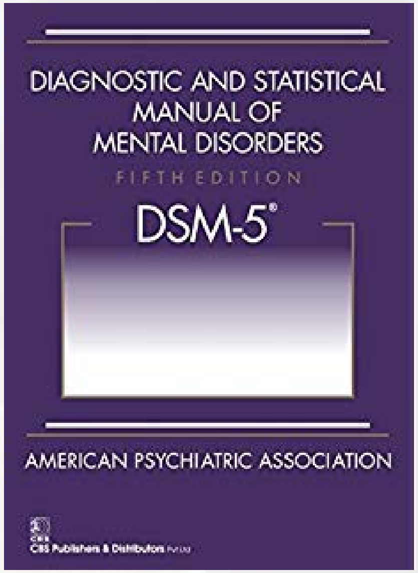
Alcohol Use Disorder

Prevalence



Alcohol-Related Disorders

Alcohol Use Disorder
Alcohol Intoxication
Alcohol Withdrawal
Other Alcohol-Induced Disorders
Unspecified Alcohol-Related Disorder



DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS
FIFTH EDITION
DSM-5®
AMERICAN PSYCHIATRIC ASSOCIATION
CBS Publishers & Distributors

- Alcohol-related disorders
  - **5%** world population
- Mortality
  - **3%** of all deaths in the world are associated with severe alcohol use
- Approximately **30%** of patients do not respond to available treatments
- Serious public health problem

Laranjeira et al., 2007; Laranjeira et al. 2012; Gowing et al. 2015

Pharmacological Treatments

Main pharmacological treatments

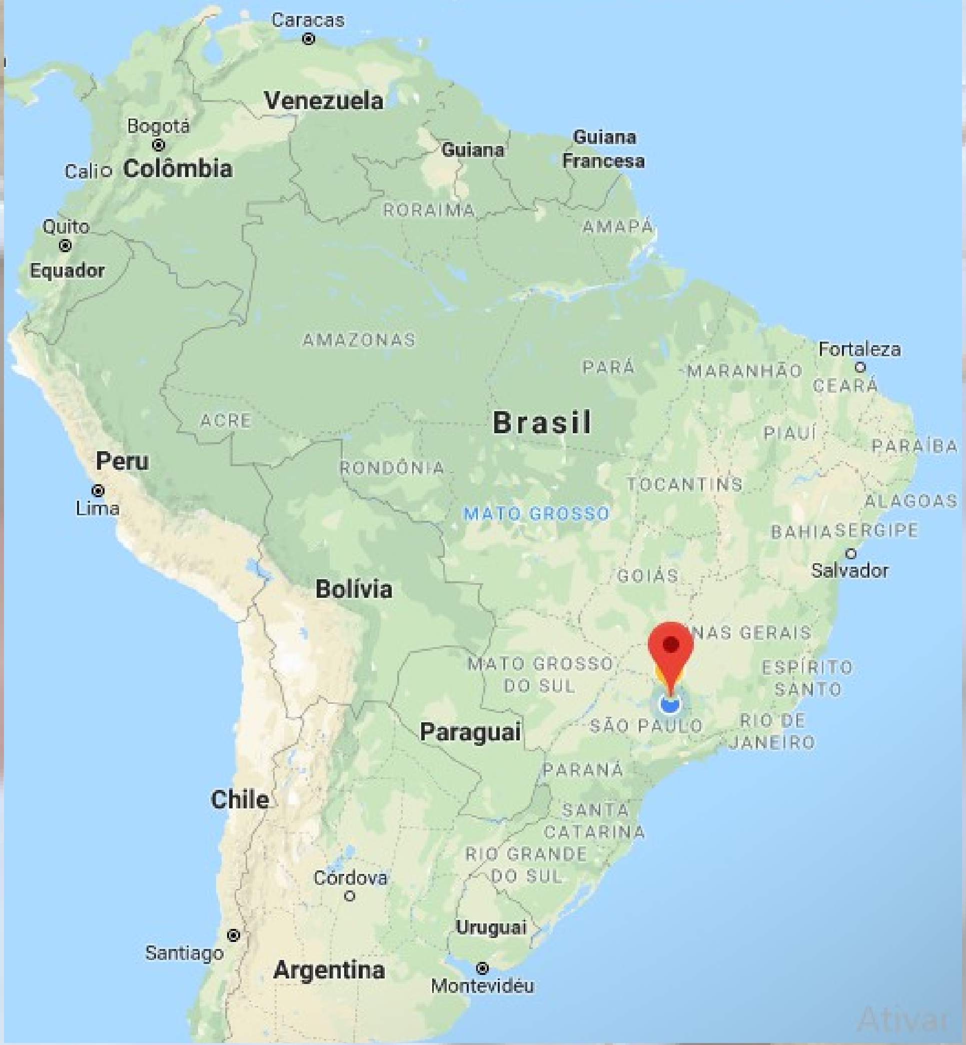
- **Acamprosate (Campral)**
    - GLU antagonist/GABA agonist: ↓ *abstinence symptoms*
    - Daily/prolonged use
    - Cardiovascular alterations, diarrhea, insomnia, impotence

- **Naltrexone (Adepend/Antaxone)**
    - Opioid antagonist: ↓ *good effects*
    - Daily/prolonged use
    - Hepatotoxicity, diarrhea, nausea

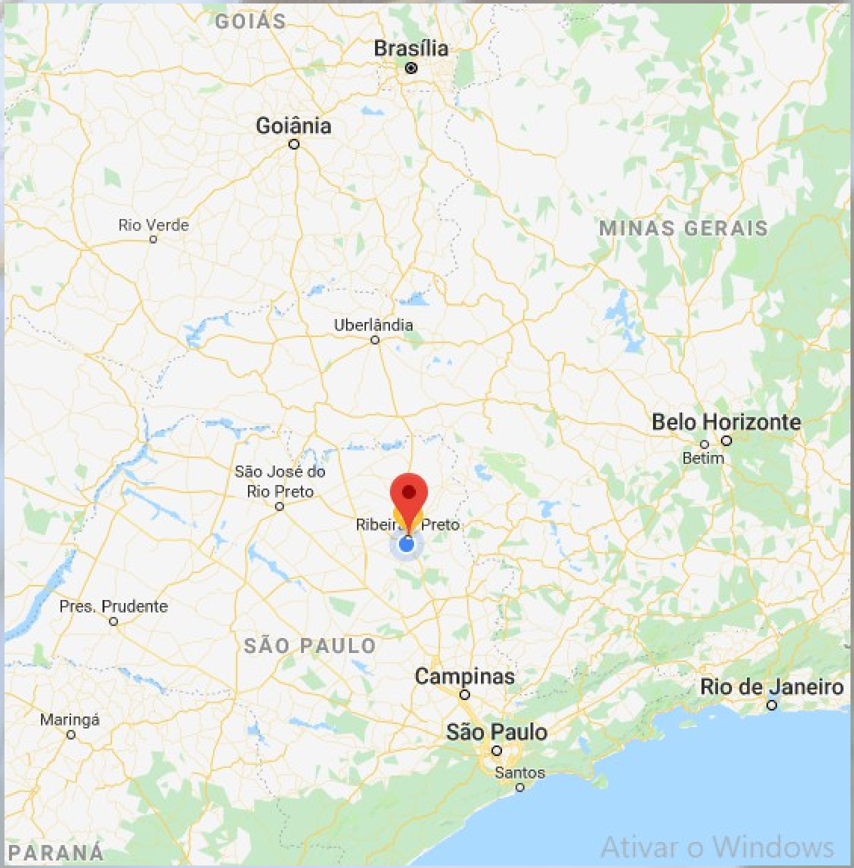
- **Disulfiram (Antabuse/Antabus)**
    - Acetaldehyde dehydrogenase inhibitor → “ *hangover effect*”
    - Daily/prolonged use
    - Hepatotoxicidade, reduces libido, overdose (+alcohol)

Heckmann & Silveira. Dependência do álcool: aspectos clínicos e diagnósticos. In: Andrade et al. *Álcool e suas consequências: uma abordagem multiconceitual*. SP, 2009.

Set & Setting



Ativar



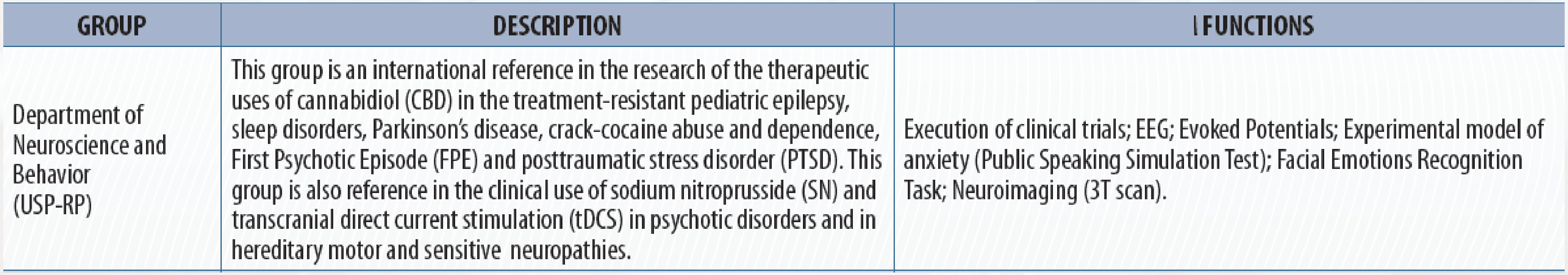
Ativar o Windows

Set & Setting

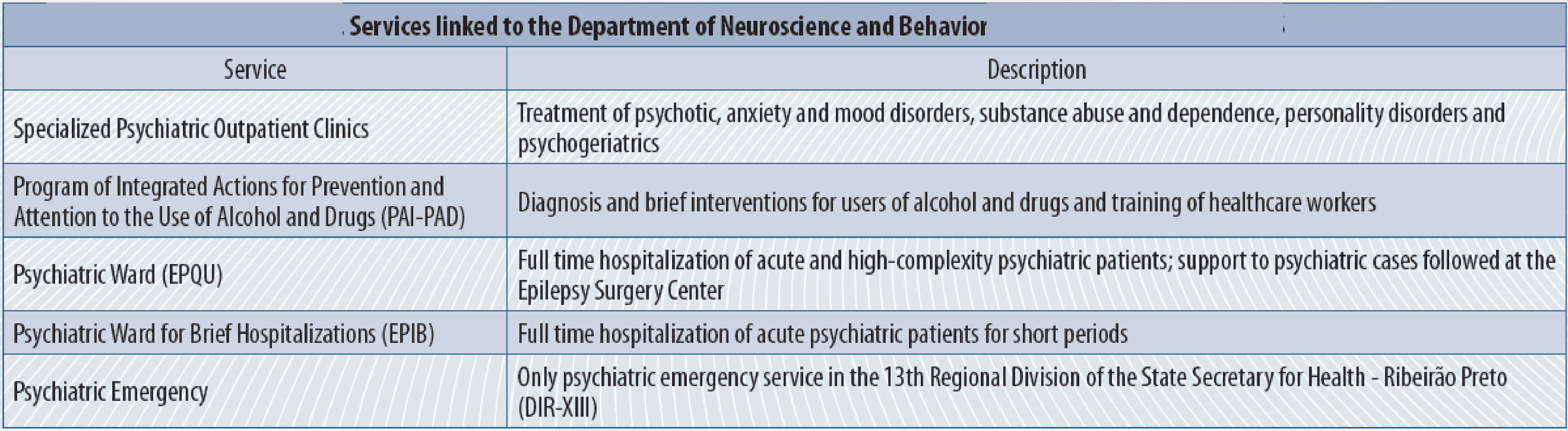
HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DE RIBEIRÃO PRETO - USP

Faculdade de Medicina de Ribeirão Preto
Universidade de São Paulo

Set & Setting

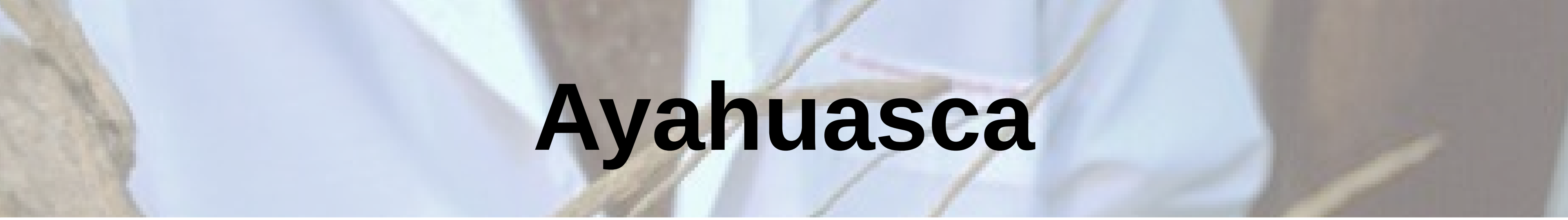


GROUP	DESCRIPTION	FUNCTIONS
Department of Neuroscience and Behavior (USP-RP)	This group is an international reference in the research of the therapeutic uses of cannabidiol (CBD) in the treatment-resistant pediatric epilepsy, sleep disorders, Parkinson's disease, crack-cocaine abuse and dependence, First Psychotic Episode (FPE) and posttraumatic stress disorder (PTSD). This group is also reference in the clinical use of sodium nitroprusside (SN) and transcranial direct current stimulation (tDCS) in psychotic disorders and in hereditary motor and sensitive neuropathies.	Execution of clinical trials; EEG; Evoked Potentials; Experimental model of anxiety (Public Speaking Simulation Test); Facial Emotions Recognition Task; Neuroimaging (3T scan).



Services linked to the Department of Neuroscience and Behavior

Service	Description
Specialized Psychiatric Outpatient Clinics	Treatment of psychotic, anxiety and mood disorders, substance abuse and dependence, personality disorders and psychogeriatrics
Program of Integrated Actions for Prevention and Attention to the Use of Alcohol and Drugs (PAI-PAD)	Diagnosis and brief interventions for users of alcohol and drugs and training of healthcare workers
Psychiatric Ward (EPQU)	Full time hospitalization of acute and high-complexity psychiatric patients; support to psychiatric cases followed at the Epilepsy Surgery Center
Psychiatric Ward for Brief Hospitalizations (EPIB)	Full time hospitalization of acute psychiatric patients for short periods
Psychiatric Emergency	Only psychiatric emergency service in the 13th Regional Division of the State Secretary for Health - Ribeirão Preto (DIR-XIII)



Ayahuasca

Psychological Medicine (2018).

Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial

Fernanda Palhano-Fontes[1,2], Dayanna Barreto[2,3], Heloisa Onias[1,2],
Katia C. Andrade[1,2], Morgana M. Novaes[1,2], Jessica A. Pessoa[1,2],
Sergio A. Mota-Rolim[1,2], Flávia L. Osório[4,5], Rafael Sanches[4,5],
Rafael G. dos Santos[4,5], Luís Fernando Tófoli[6], Gabriela de Oliveira Silveira[7],
Mauricio Yonamine[7], Jordi Riba[8], Francisco R. Santos[9], Antonio A. Silva-Junior[9],
João C. Alchieri[10], Nicole L. Galvão-Coelho[5,11], Bruno Lobão-Soares[5,12],
Jaime E. C. Hallak[4,5], Emerson Arcoverde[2,3,5], João P. Maia-de-Oliveira[2,3,5]
and Dráulio B. Araújo[1,2]

Prof. Jaime Hallak

Prof. Draulio de Araujo

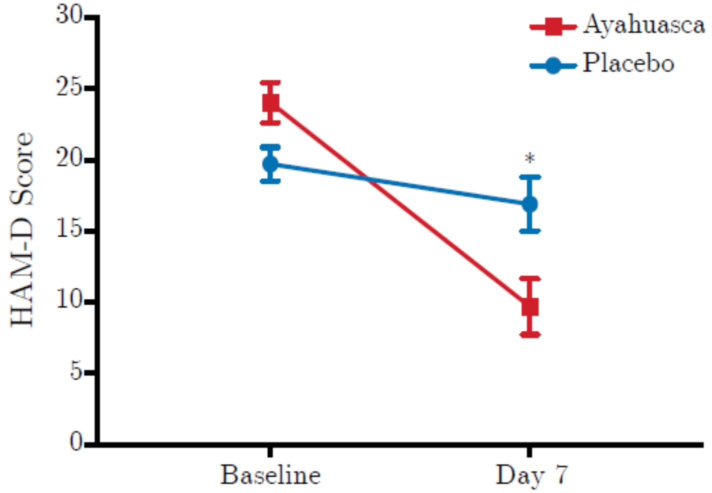


Figure 2. HAM-D scores at baseline and seven days after dosing.

(n = 29)

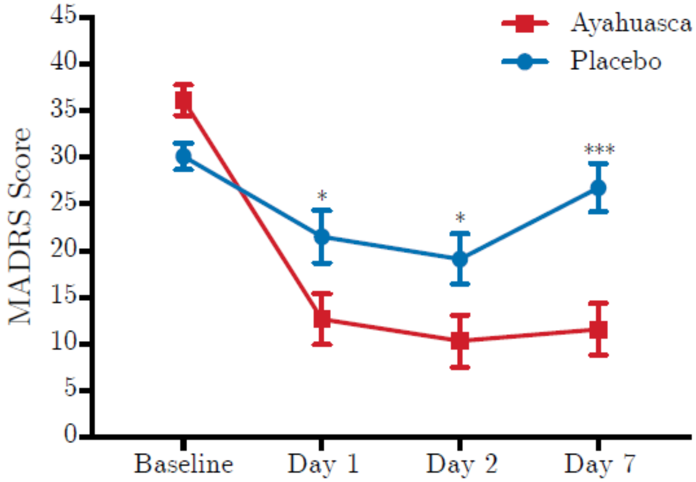
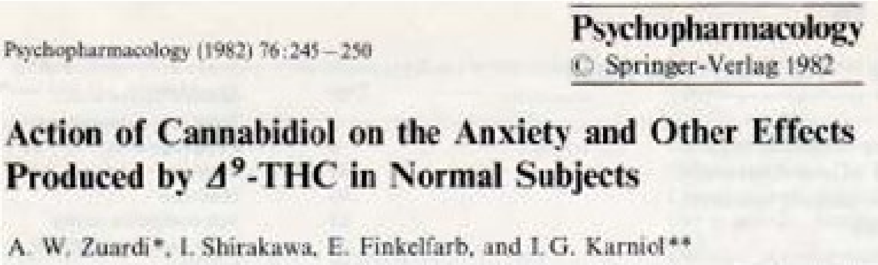


Figure 3. MADRS scores as a function of time.

Cannabidiol (CBD)

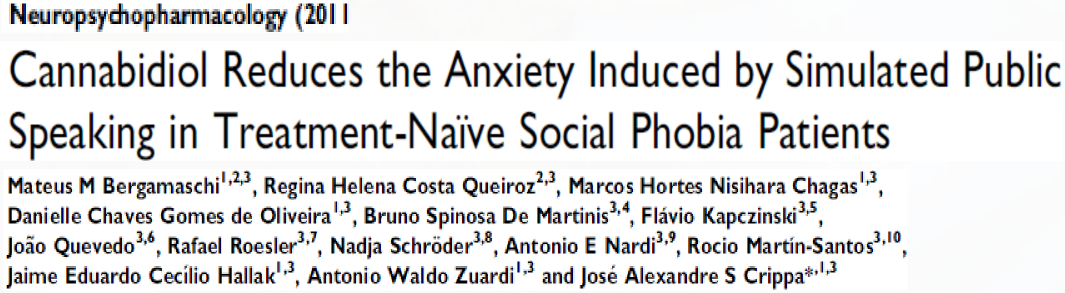


Psychopharmacology (1982) 76:245–250

Psychopharmacology
© Springer-Verlag 1982

Action of Cannabidiol on the Anxiety and Other Effects Produced by Δ^9-THC in Normal Subjects

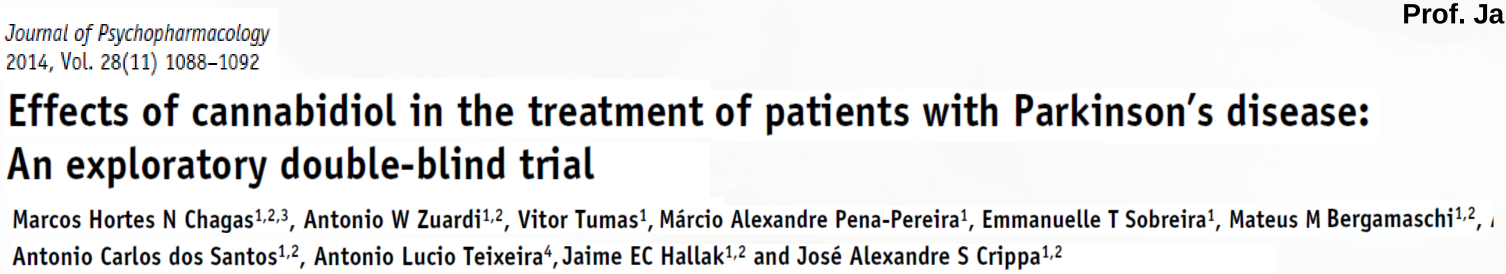
A. W. Zuardi*, I. Shirakawa, E. Finkelfarb, and I. G. Karniol**



Neuropsychopharmacology (2011

Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

Mateus M Bergamaschi[1,2,3], Regina Helena Costa Queiroz[2,3], Marcos Hortes Nisihara Chagas[1,3], Danielle Chaves Gomes de Oliveira[1,3], Bruno Spinosa De Martinis[3,4], Flávio Kapczinski[3,5], João Quevedo[3,6], Rafael Roesler[3,7], Nadja Schröder[3,8], Antonio E Nardi[3,9], Rocio Martín-Santos[3,10], Jaime Eduardo Cecílio Hallak[1,3], Antonio Waldo Zuardi[1,3] and José Alexandre S Crippa*[,1,3]



Journal of Psychopharmacology
2014, Vol. 28(11) 1088–1092

Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial

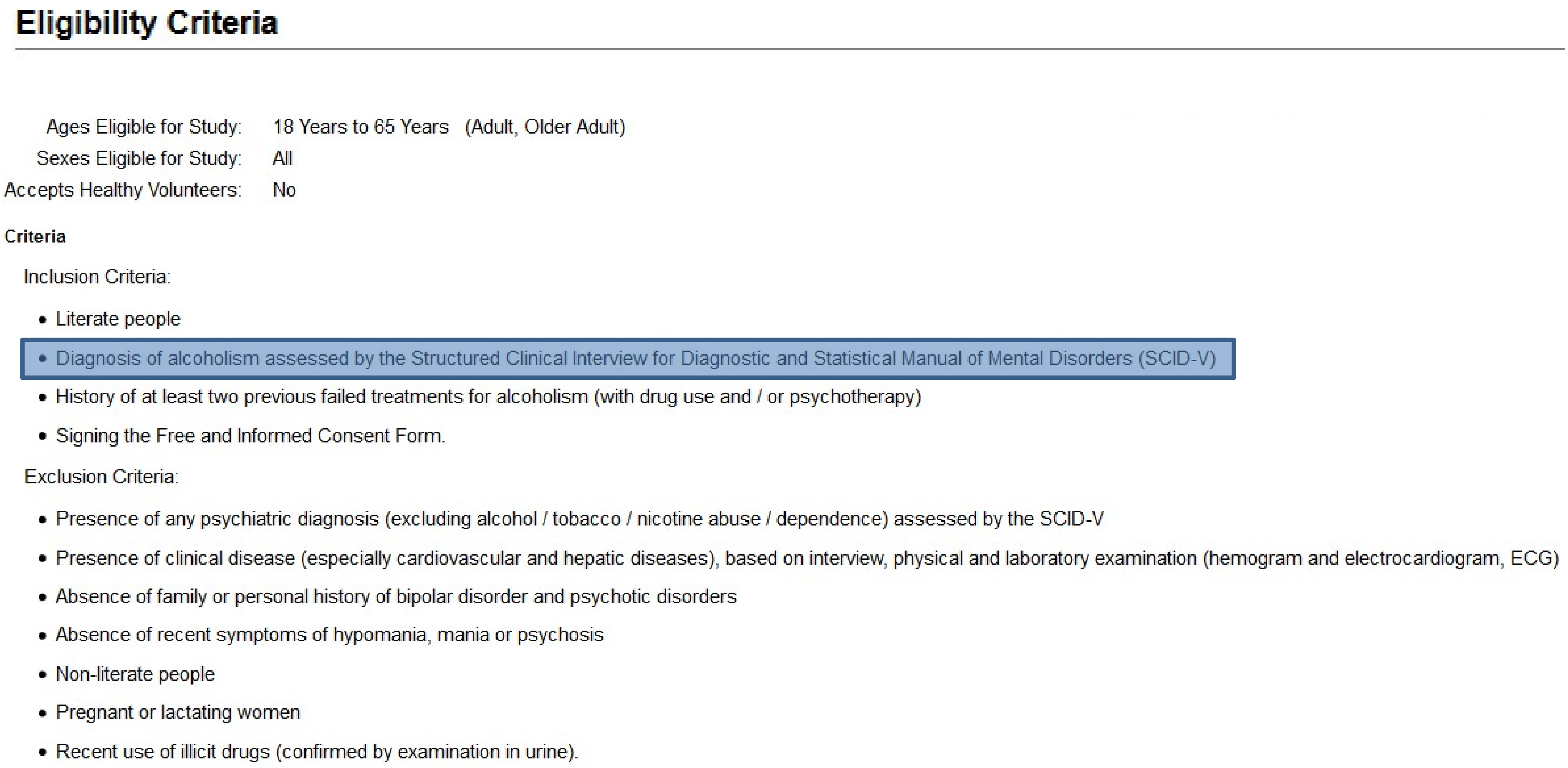
Marcos Hortes N Chagas[1,2,3], Antonio W Zuardi[1,2], Vitor Tumas[1], Márcio Alexandre Pena-Pereira[1], Emmanuelle T Sobreira[1], Mateus M Bergamaschi[1,2],
Antonio Carlos dos Santos[1,2], Antonio Lucio Teixeira[4], Jaime EC Hallak[1,2] and José Alexandre S Crippa[1,2]

Prof. Antônio Zuardi

Prof. José Alexandre Cripp

Prof. Jaime Hallak

Ibogaine: Study Design



Eligibility Criteria

Ages Eligible for Study:	18 Years to 65 Years (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

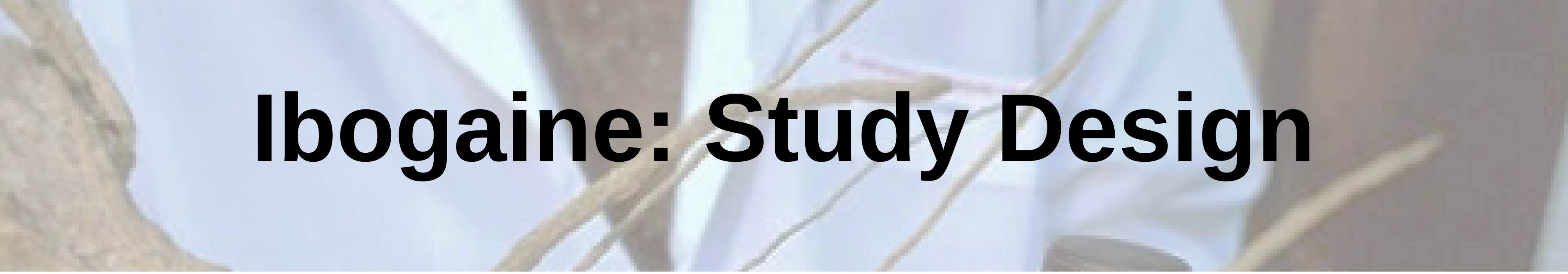
Criteria

Inclusion Criteria:

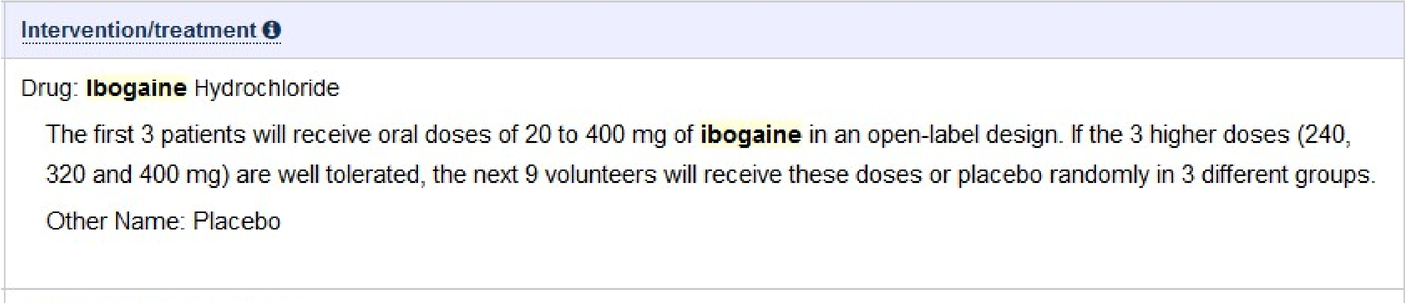
- Literate people
- Diagnosis of alcoholism assessed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID-V)
- History of at least two previous failed treatments for alcoholism (with drug use and / or psychotherapy)
- Signing the Free and Informed Consent Form.

Exclusion Criteria:

- Presence of any psychiatric diagnosis (excluding alcohol / tobacco / nicotine abuse / dependence) assessed by the SCID-V
- Presence of clinical disease (especially cardiovascular and hepatic diseases), based on interview, physical and laboratory examination (hemogram and electrocardiogram, ECG)
- Absence of family or personal history of bipolar disorder and psychotic disorders
- Absence of recent symptoms of hypomania, mania or psychosis
- Non-literate people
- Pregnant or lactating women
- Recent use of illicit drugs (confirmed by examination in urine).



Ibogaine: Study Design



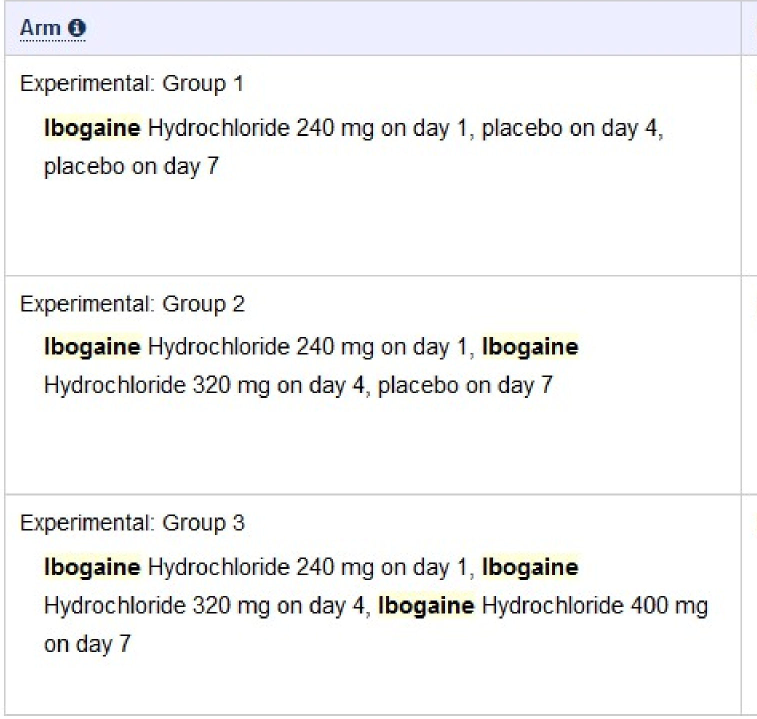
Intervention/treatment

Drug: **Ibogaine** Hydrochloride

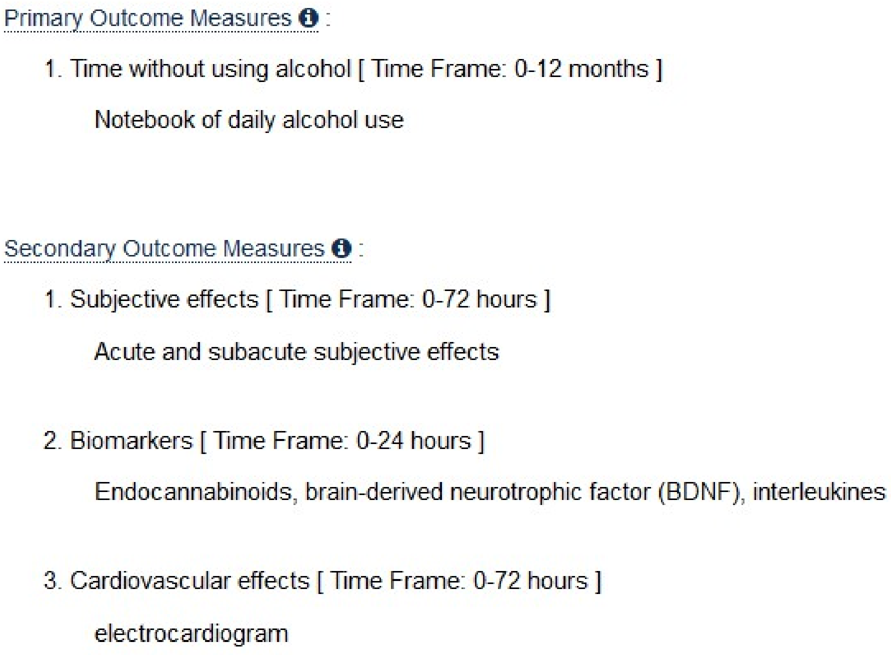
The first 3 patients will receive oral doses of 20 to 400 mg of **ibogaine** in an open-label design. If the 3 higher doses (240, 320 and 400 mg) are well tolerated, the next 9 volunteers will receive these doses or placebo randomly in 3 different groups.

Other Name: Placebo

Phytostan do Brasil Ltda



Arm
Experimental: Group 1 **Ibogaine** Hydrochloride 240 mg on day 1, placebo on day 4, placebo on day 7
Experimental: Group 2 **Ibogaine** Hydrochloride 240 mg on day 1, **Ibogaine** Hydrochloride 320 mg on day 4, placebo on day 7
Experimental: Group 3 **Ibogaine** Hydrochloride 240 mg on day 1, **Ibogaine** Hydrochloride 320 mg on day 4, **Ibogaine** Hydrochloride 400 mg on day 7



Primary Outcome Measures :

1. Time without using alcohol [Time Frame: 0-12 months]

   Notebook of daily alcohol use

Secondary Outcome Measures :

1. Subjective effects [Time Frame: 0-72 hours]

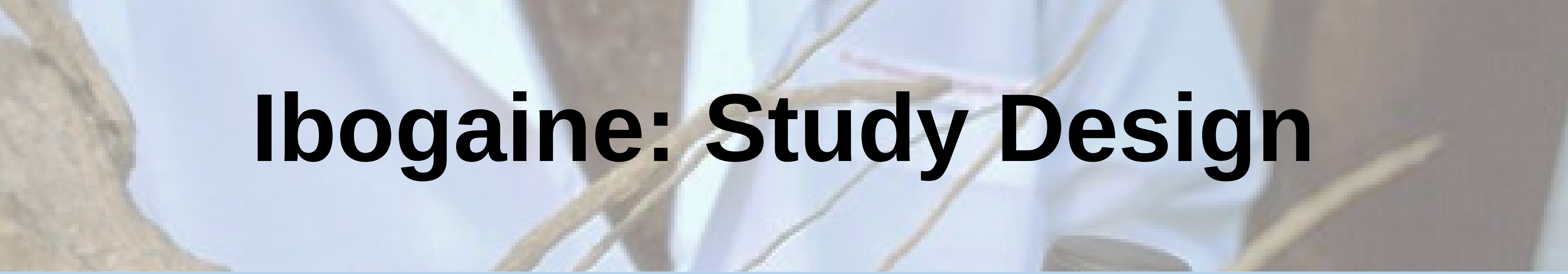
   Acute and subacute subjective effects

2. Biomarkers [Time Frame: 0-24 hours]

   Endocannabinoids, brain-derived neurotrophic factor (BDNF), interleukines

3. Cardiovascular effects [Time Frame: 0-72 hours]

   electrocardiogram



Ibogaine: Study Design

1- Internação e síndrome de abstinência (dias 1-5)

- Hemograma completo (HEM): 8:00 (basal) e dia 3
- Urina (drogas, gravidez): basal
- HADS: basal
- Eletrocardiograma (ECG), escala para avaliação da síndrome de abstinência (CIWA-Ar), BPRS: (basal) e 12 h após (dias 1-3)

2- Sessão ibogaína 1 (dia 6)

- Urina (drogas, gravidez): 7:30
- ECG: 8:00 (basal) e 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48 e 72 h após a administração de ibogaína
- VAMS, ESS, BPRS, CADSS: basal e 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 h após a administração de ibogaína
- HADS: basal
- Administração de ibogaína: 9:00 (Vol 1: 20 mg; Vol 2: 80 mg; Vol 3: 240 mg; Vols 4-12: 240 mg)
- UKU: 12, 24 e 72 h após a administração de ibogaína

3- Sessão ibogaína 2 (dia 11)

- Urina (drogas, gravidez): 7:30
- ECG: 8:00 (basal) e 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48 e 72 h após a administração de ibogaína
- VAMS, ESS, BPRS, CADSS: basal e 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 h após a administração de ibogaína
- Administração de ibogaína: 9:00 (Vol 1: 40 mg; Vol 2: 160 mg; Vol 3: 320 mg; Vols 4-12: placebo ou 320 mg)
- UKU: 12, 24 e 72 h após a administração de ibogaína

4- Sessão ibogaína 3 (dia 15)

- Urina (drogas, gravidez): 7:30
- ECG: 8:00 (basal) e 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48 e 72 h após a administração de ibogaína
- VAMS, ESS, BPRS, CADSS: basal e 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 h após a administração de ibogaína
- Administração de ibogaína: 9:00 (Vol 1: 80 mg; Vol 2: 240 mg; Vol 3: 400 mg; Vols 4-12: placebo ou 400 mg)
- UKU: 12, 24 e 72 h após a administração de ibogaína

5- Saída do hospital (dia 20)

- ECG, BPRS, CADSS, HADS, UKU: 8:00

6- Seguimento (7, 14 e 21 dias e 1, 3, 6 e 12 meses após sair do hospital)

- ECG, BPRS, CADSS, HADS, UKU, CUA: 8:00

7- Final do tratamento (12 meses após sair do hospital)

- SATMED-Q

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